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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/544,093	03/03/2006	Ted Yednock	15270J-009820US	6443

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EXAMINER	
EMCH, GREGORY S	

ART UNIT	PAPER NUMBER
1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/544,093	YEDNOCK ET AL.	
	Examiner	Art Unit	
	Gregory S. Emch	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 July 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *103,105-113,118 and 120-140* is/are pending in the application.

4a) Of the above claim(s) *128-131,139 and 140* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *103,105-113,118,120-127 and 132-138* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to amendment

Claims 106 and 121 have been amended as requested in the amendment filed on 22 July 2010. Following the amendment, claims 103, 105-113, 118, and 120-140 are pending in the instant application.

Claims 128-131, 139 and 140 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 17 November 2008.

Claims 103, 105-113, 118, 120-127 and 132-138 are under examination in the instant office action.

Withdrawn Objections/Rejections

The objection to claims 106 and 121 is withdrawn in response to the amendments to said claims which corrected their grammar.

Remaining issues are set forth below.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 103, 108, 109, 112, 113, 118, 123, 124, 127 and 132 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Selkoe (U.S. Patent 5,262,332, Citation 951 on IDS dated 17 November 2008), Solomon 1996 (Proc Natl Acad Sci USA 93:452-455, Citation 160 on IDS dated 01 August 2005) and Nordstedt (WO 97/21728, Citation 202 on IDS dated 01 August 2005) and Penney (U.S. Patent 5,773,007, Citation 1148 on IDS dated 07 July 2009).

Selkoe teaches methods of making antibodies to Aβ (beta amyloid protein or β-AP) that are to be used for detection and diagnosis of disease. Specifically, at col.2 lines 36-44, Selkoe teaches methods of diagnosing Alzheimer's disease by contacting samples from patients with antibodies that are capable of identifying β-AP or "a β-AP fragment of about 8 or more amino acids". At col.3 line 51 – col. 4, line 24, Selkoe teaches that fragments of "about 8 or more amino acid residues" can be used to make antibodies to β-AP. Thus, the reference is on point to products for making antibodies that bind to Aβ consisting of fragments of "about 8" amino acids of β-AP. Selkoe teaches that up to 250 µg of protein can be administered with pharmaceutically acceptable carriers for production of antibodies (col.17 lines 34-40), which is on point to claims 113, 118, 123, 124 and 127. However, Selkoe does not teach the claimed fragment of Aβ linked to a carrier.

Solomon teaches antibodies which bind to aggregating epitopes of Aβ, i.e. those regions within the protein which induce formation of fibrils or aggregates. Solomon provides *in vitro* data on the efficacy of antibodies and suggests that they should be administered to patients for treatment of Alzheimer's disease; see for example p.454 second column, last three paragraphs. However Solomon does not explicitly teach administration of antibodies to patients, and does not explicitly identify the claimed residues 16-23 as those to which the antibody should bind.

Nordstedt teaches that the sequence "KLVFF", which corresponds to residues 16-20 of Aβ is required for the polymerization, or aggregation, of Aβ protein and subsequent formation of fibrils (see, for example, p. 3 final paragraph which states this

sequence is necessary for fibril formation to occur as well as p. 16 lines 7-15 which reiterates the finding). Nordstedt also teaches that compounds which bind to this sequence should be used to inhibit polymerization of Aβ peptide, as is desired for treatment of Alzheimer's disease (see p. 8, lines 12 – 20). Nordstedt does not explicitly teach antibodies which bind to this sequence, nor antibodies linked to a carrier molecule.

Penney teaches that purified antigens are often not effective in eliciting an antibody response, and so to boost the response one should include an immunostimulant, as in claim 103 (see col.1 line 63 – col.2, line 8). Penney teaches that any carrier molecule can be used, including Keyhole Limpet Hemocyanin (KLH), as in claims 109 and 124, and any of several toxoids from pathogenic bacteria, including but not limited to CRM 197, which is a diphtheria toxioid, as in claims 112 and 127 (see col.5, first paragraph). Penney teaches covalent linkage, and is thus on point to claims 108, 123, and 132; see col.1 lines 8-12 and col.5, first paragraph, for example. Penney does not teach conjugates comprising residues 16-23 of Aβ as claimed.

However, at the time the invention was made, it would have been obvious to one of ordinary skill in the art to make a composition comprising residues 16-23 of Aβ peptide covalently linked to an immunostimulant carrier as claimed, with a reasonable expectation of success. The motivation to do so would be to stimulate the host animal's immune system to make more antibodies, as taught by Penney, which could then be used in the diagnostic assays of either Selkoe or in the treatment methods of Solomon. Selkoe teaches that "about 8" amino acids should be used in raising antibodies, and

Solomon and Nordstedt point to the region of Aβ the protein at residues 16-20. Solomon and Nordstedt taken together guide the artisan of ordinary skill to select antibodies against this particular epitope for treatment of Alzheimer's, as Solomon teaches antibodies against aggregating epitopes should be used, and Nordstedt specifically teaches that residues 16-20 constitute such an aggregating epitope. The artisan of ordinary skill would then be motivated to use residues 16-23 in place of residues 16-20 given Selkoe's explicit teaching that 8 amino acids should be used to successfully raise antibodies. Furthermore, given Penney's teachings to include an immunostimulant carrier to increase antigenicity, the artisan would have had a reasonable to expectation of success in producing antibodies.

In the reply filed on 22 July 2010, applicants assert that although Selkoe teaches that some fragments of about 8 or more amino acids from Aβ are capable of producing antibodies, he also reports that antibodies raised against amyloid deposits showed stronger staining than an antibody to a synthetic peptide containing residues 1-28 of Aβ. Applicants assert that this teaching would have discouraged the use of small synthetic fragments of Aβ for generating antibodies for diagnosis or therapy and that one of skill in the art would have instead have selected an antibody raised against Aβ deposits.

Applicants' arguments have been fully considered and are not found persuasive. According to applicants' logic, the only way to treat or diagnose Alzheimer's disease is by using antibodies to amyloid deposits. On the contrary, Selkoe explicitly teaches methods of diagnosing Alzheimer's disease by contacting samples from patients with

antibodies that are capable of identifying β-AP or "a β-AP fragment of about 8 or more amino acids". Applicants' assertion regarding Selkoe's antibodies concerns Selkoe's disclosure at col.21, lines 13-18. Immediately following this teaching, i.e. at col.21, lines 18-26, Selkoe states, "However, the latter synthetic fragment of the β-AP (comprising amino acids 1-28) or smaller β-AP fragments of 8 or more amino acids, can be used as immunogens to produce peptide antibodies that can be used to detect skin β-AP deposits in AD patients." Thus, Selkoe's teachings, when considered as a whole, provide strong motivation for using antibodies raised against Aβ peptides with as little as 8 amino acids.

Applicants assert that it would not have been obvious to modify Solomon to use active immunization to generate antibodies because Solomon discusses experiments to assess the effect of antibodies to Aβ on aggregation and neurotoxicity of Aβ *in vitro*. Applicants assert that Solomon concludes by discussing gene therapy as a means to deliver nucleic acids encoding antibody fragments. Applicants assert that Solomon's proposed mechanism of inhibition of aggregation is one of antibody binding without a role for the antibody effector system (i.e., antibody-dependent cell-mediated cytoxicity ("ADCC") or complement-dependent cell-mediated cytoxicity ("CDCC")). Applicants assert that Solomon's proposal to use antibody fragments is consistent with such a mechanism in that the effector or constant region of the antibody is largely or entirely absent in antibody fragments. Thus, applicants assert that switching from passive delivery of antibody fragments to active immunization with peptide fragments would not have been obvious from Solomon's disclosure because the antibodies generated from

active immunization would be intact antibodies with effector regions, which would potentially induce inflammation.

Applicants' arguments have been fully considered and are not found persuasive. Applicants are reminded that the claims are directed to a product, i.e. a fragment of Aβ, the amino acid sequence of which consists of KLVFFAED (residues 16-23 of SEQ ID NO: 1): wherein the fragment is linked to a carrier molecule to form a conjugate which helps elicit an immune response against the fragment. The claims are not directed to methods of active immunization for treatment of Alzheimer's. The claimed invention is also suitable for use in antibody production in an animal, wherein the inflammation is necessary for sufficient antibody titers. Here, one of skill in the art would not be concerned with avoiding ADDC or CDCC for treatment. Regardless, the portion of Solomon that applicants' cite, i.e. p.454, last paragraph, merely mentions gene therapy as a recent advance in antibody engineering; Solomon's disclosure is not limited to gene therapy of antibody fragments.

Applicants allege that Nordstedt can not be cited as fully representative of the thinking of those of skill in the art at the effective filing date of the present application because the art as a whole did not point to the 16-20 region of Aβ as being the key region to focus therapeutic treatments. Applicants submit that other art references point away from this region. Applicants assert that Penney does not add to the teaching of the other references cited in the instant rejection regarding selecting Aβ16-23 in particular.

Applicants' arguments have been fully considered and are not found persuasive.

Regardless of whether other prior art references did not point to the 16-20 region of Aβ as being the key region to focus therapeutic treatments, Nordstedt explicitly teaches this region of Aβ is required for the polymerization, or aggregation, of Aβ protein and subsequent formation of fibrils (see, for example, p. 3 final paragraph which states this sequence is necessary for fibril formation to occur and p. 16, lines 7-15 which reiterates the finding). Nordstedt also explicitly teaches that compounds which bind to this sequence should be used to inhibit polymerization of Aβ peptide, as is desired for treatment of Alzheimer's disease (see p. 8, lines 12-20). Given Nordstedt's explicit teaching, it would have been obvious to try to target this region to produce antibodies. Only a reason, suggestion or motivation need appear in the cited prior art in order to combine references under 35 U.S.C. 103. Pro Mold Tool Col. v. Great Lakes Plastics, Inc., 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996). Therefore, the combination of the prior art references of record is deemed proper, and the instant rejection under 35 U.S.C. 103(a) is maintained.

Claims 105 and 120 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Selkoe, Solomon, Nordstedt and Penney as applied to claims 103, 108, 109, 112, 113, 118, 123, 124, 127, and 132 above, and further in view of Restifo (U.S. Patent 5,733,548, Citation 770 on IDS dated 09 March 2008).

The reasons why claims 103, 108, 109, 112, 113, 118, 123, 124, 127, and 132 are obvious over Selkoe, Solomon, Nordstedt and Penney are set forth above.

However none of the references explicitly teaches a plurality of additional copies of the relevant antigen, as recited in claims 105 and 120.

Restifo discloses that multiple copies of a peptide can be included in order to increase the immunogenicity of said peptide, and that this method should be effective even in those cases where a single copy of the peptide itself is not antigenic (see col.4, lines 32-36 and col.5, lines 15-22). Thus, the reference is on point to claims 105 and 120. However, Restifo does not teach residues 16-23 of Aβ as claimed.

It would have been obvious to one of ordinary skill in the art to include multiple copies of the antigen, as suggested by Restifo, with a reasonable expectation of success. The motivation to do so would be to increase the immune response to the peptide antigen. The artisan of ordinary skill would realize that a small peptide (i.e. one that is 8 amino acids long as taught by Selkoe) would be unlikely to elicit a strong immune response on its own, since Selkoe teaches that this is the minimum length that should be used. Thus, the artisan would have been motivated to include multiple copies of the antigen and would have found such an invention obvious.

In the reply filed on 22 July 2010, applicants assert that Restifo does not cure the deficiencies of the primary cited references.

Applicants' arguments have been fully considered and are not found persuasive. The primary references are not considered deficient, and the instant rejection is deemed proper.

Claims 106, 107, 110, 111, 121, 122, 125, 126, 133-135, 137 and 138 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Selkoe, Solomon, Nordstedt and Penney as applied to claims 103, 108, 109, 112, 113, 118, 123, 124, 127, and 132 above, and further in view of WO 00/72876 A2 to Schenk (citation 323 on IDS dated 01 August 2005).

The reasons why claims 103, 108, 109, 112, 113, 118, 123, 124, 127, and 132 are obvious over Selkoe, Solomon, Nordstedt and Penney are set forth above. However none of Selkoe, Solomon, Nordstedt, or Penney teaches the specific adjuvants of claims 106, 107, 110, 111, 121, 125, 126, 133 or 135.

Schenk teaches that preferred carriers for use in Aβ immunizing compositions are the T cell epitopes that comprise the instant SEQ ID NO: 8 or SEQ ID NO: 11 (see Sequence alignments B and C from previous office action dated 09 February 2009, and p.43, lines 14 and 19 of the '876 document), as in claims 110, 111, 125 and 126. Schenk further teaches that multiple copies of the carrier can be included (p.44, lines 9-11), as in claims 106 and 121. Schenk teaches that the fragment can be linked to the carrier through a spacer (p.43, line 28 – p.44, line 5), as in claims 107 and 122. Schenk teaches the adjuvants alum, MPL and QS-21 and is thus on point to claims 133-135 (see p.53, lines 16-17 and 30) and teaches surfactants included in the pharmaceutical compositions (p.55, line 29), as in claim 137. Schenk teaches including the peptide and adjuvant as a pharmaceutical composition in a vial and is thus on point to claim 138 (see p.54, lines 23-26).

It would have been obvious to one of ordinary skill in the art to select the claimed carriers taught by Schenk as adjuvants to be included in the compositions rendered obvious by Selkoe, Solomon, Nordstedt and Penney with a reasonable expectation of success. The motivation to do so would be to select an adjuvant known to be particularly effective in eliciting antibodies, which could then be used in the methods taught by Selkoe or by Solomon.

In the reply filed on 22 July 2010, applicants assert that Schenk does not cure the deficiencies of the primary cited references.

Applicants' arguments have been fully considered and are not found persuasive. The primary references are not considered deficient, and the instant rejection is deemed proper.

Claim 136 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Selkoe, Solomon, Nordstedt and Penney as applied to claims 103, 108, 109, 112, 113, 118, 123, 124, 127, and 132 above, and further in view of WO 01/78777 A2 to Mossman et al. (Cited on PTO-892 dated 09 February 2009).

The reasons why claims 103, 108, 109, 112, 113, 118, 123, 124, 127, and 132 are obvious over Selkoe, Solomon, Nordstedt and Penney are set forth above. However none of Selkoe, Solomon, Nordstedt, or Penney teaches the specific adjuvant of claim 136.

Mossman teaches that a preferred adjuvant is RC-529 (e.g. abstract), as in claim 136.

It would have been obvious to one of ordinary skill in the art to select the claimed RC-529 taught by Mossman as the adjuvant to be included in the compositions rendered obvious by Selkoe, Solomon, Nordstedt and Penney with a reasonable expectation of success. The motivation to do so would be to select an adjuvant known to be particularly effective in eliciting antibodies, which could then be used in the methods taught by Selkoe or by Solomon.

In the reply filed on 22 July 2010, applicants assert that Mossman does not cure the deficiencies of the primary cited references.

The primary references are not considered deficient and therefore, the instant rejection is deemed proper.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregory S. Emch whose telephone number is (571) 272-8149. The examiner can normally be reached 9:00 am - 5:30 pm EST (M-F).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey J. Stucker can be reached at (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.
/G.E./

Gregory S. Emch
Patent Examiner
Art Unit 1649
07 October 2010

/Daniel E Kolker/
Primary Examiner, Art Unit 1649
October 12, 2010